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Environmental Protection Agency

Office of Emergency and Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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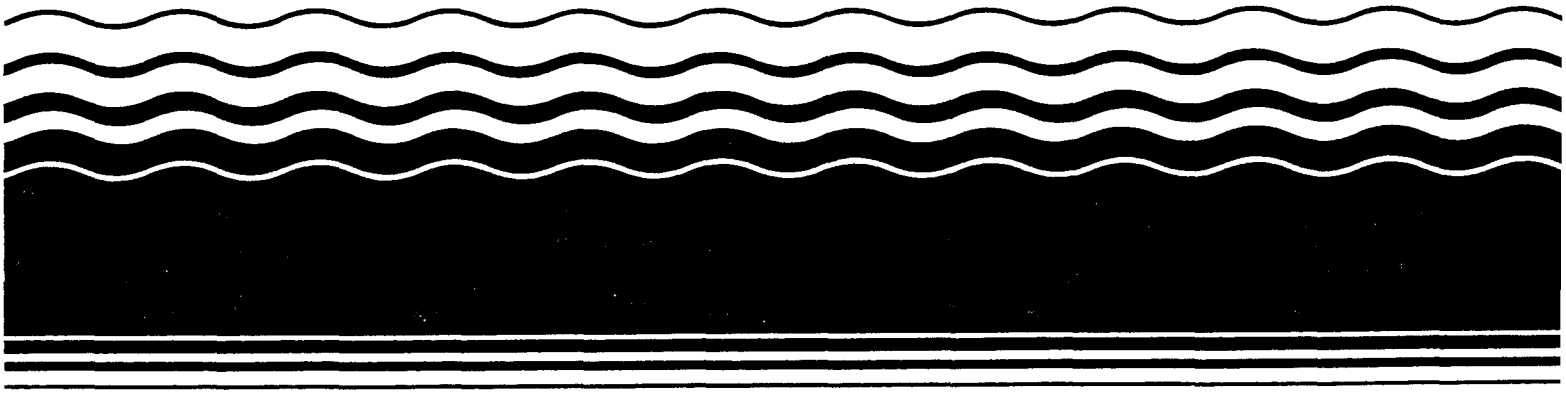
HEALTH EFFECTS ASSESSMENT FOR METHYL ETHYL KETONE



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U.S. Environmental Protection Agency
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DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with methyl ethyl ketone. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

A number of subchronic inhalation studies in experimental animals are available which suggest threshold exposure levels for liver damage and neurological impairment. An AIS for inhalation of 153.4 mg/day is estimated from these studies. No chronic exposure data are available; therefore, an AIC of 15.3 mg/day has been estimated based on the subchronic studies. This estimate should be reviewed when adequate chronic data become available. No information concerning consequences of oral exposure to methyl ethyl ketone could be located. As a result, neither a AIS or AIC for oral exposure are presented. A CS of 8.8 was calculated for methyl ethyl ketone based on fetotoxicity in rats exposed by inhalation.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CS	Composite score
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of methyl ethyl ketone (CAS No. 78-93-3) are summarized below:

Chemical class:	aliphatic ketone	
Molecular weight:	72.1	Verschueren, 1983
Vapor pressure at 20°C:	77.5 mm Hg	Verschueren, 1983
Water solubility at 20°C:	268 g/ℓ	Lande et al., 1976
Log octanol/water partition coefficient:	0.26	Verschueren, 1983
Bioconcentration factor:	0.33 (estimated)	
Half-life in air:	14 hours	Graedel, 1978
Half-life in water:	~ days	Lande et al., 1976

The BCF for methyl ethyl ketone was estimated from the octanol/water partition coefficient value given in the table and the regression equation developed by Veith et al. (1979).

The half-life of methyl ethyl ketone in aquatic media was not located in the available literature. However, in most surface waters, this compound may biodegrade almost completely within 10 days (Lande et al., 1976). The evaporative half-life from water was calculated to be ~6 days (Lande et al., 1976). However, use of the Mackay and Wolkoff (1973) equation for estimating the evaporative half-life of this compound, which cannot be classified as "slightly soluble," remains questionable.

Pertinent data regarding the fate and transport of methyl ethyl ketone in soil could not be located in the available literature. Based on its relatively high water solubility and low octanol/water partition coefficient, methyl ethyl ketone is expected to have a high soil mobility.

The two other processes that may account for the significant loss of methyl ethyl ketone from soil are volatilization and biodegradation. By analogy from aquatic media, the half-life of methyl ethyl ketone in soils can be speculated to be about a few days.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative data on the oral absorption of methyl ethyl ketone are not available, but absorption from the GI tract can be inferred from systemic toxic effects observed after acute oral administration (Lande et al., 1976).

2.2. INHALATION

Quantitative data on the pulmonary absorption of methyl ethyl ketone are not available, but absorption from the lungs can be inferred from systemic toxic effects observed after acute and subchronic inhalation exposures (Lande et al., 1976).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the effects on humans or experimental animals of oral exposure to methyl ethyl ketone could not be located in the available literature.

3.1.2. Inhalation. The subchronic inhalation studies on methyl ethyl ketone are summarized in Table 3-1. Cavender et al. (1983) exposed both sexes of rats to methyl ethyl ketone at concentrations of 0, 1250, 2500 or 5000 ppm, 6 hours/day, 5 days/week, for 90 days. There were no treatment-related effects at the 1250 ppm level; SGPT activity in female rats was elevated at the 2500 ppm level. At the 5000 ppm level, effects were more severe and included depressed mean body weight; slight but significant increases in liver weight, liver-to-body weight ratio, and liver-to-brain weight ratio; significantly decreased SGPT activity; and increased alkaline phosphatase, potassium and glucose values in treated females. A NOAEL for increased SGPT activity of 2500 ppm of methyl ethyl ketone can be suggested for rats from this study.

Exposure of rats to methyl ethyl ketone at a level of 200 ppm, 12 hours/day, 7 days/week for 24 weeks resulted in slight neurological effects visible only at 4 months of treatment (Takeuchi et al., 1983), but exposure of rats to 1125 ppm continuously for 5 months did not result in neuropathy, defined in terms of paralysis (Saida et al., 1976). In both studies, only a single toxicological endpoint, either motor nerve conduction velocity, mixed nerve conduction velocities, or distal motor latency (Takeuchi et al., 1983) or paralysis (Saida et al., 1976), was examined.

TABLE 3-1

Subchronic Inhalation Toxicity Testing of Methyl Ethyl Ketone*

Species/Strain	Sex	Number at Start	Exposure	Effects	Reference
Rats/F344	M/F	15/sex/ exposure level	0, 1250, 2500 or 5000 ppm, 6 hours/day, 5 days/week, for 90 days	No neuropathologic or histopathologic changes and no effect on clinical parameters or growth at the 1250 ppm level. At the 2500 ppm level, female rats had elevated SGPT activity. At the 5000 ppm level, treatment-related effects included depressed mean body weight; slight but significant increases in liver weight, liver to body weight ratio, and liver to brain weight ratio; significantly decreased SGPT activity; and increased alkaline phosphatase, K, and glucose values in treated females.	Cavender et al., 1983
Rats/Wistar	M	8/exposure level	0 or 200 ppm, 12 hours/day, 7 days/week, for 24 weeks	No effect on body weight; significantly increased motor nerve conduction velocity and mixed nerve conduction velocities after 4 weeks of exposure, but not after 24 weeks; significantly decreased distal motor latency after 4 weeks of exposure, but not after 24 weeks.	Takeuchi et al., 1983
Rats/NR	NR	NR	0 or 1125 ppm continuously for 5 months	No neuropathy, defined in terms of paralysis, was observed. No other toxicological endpoints were evaluated.	Saida et al., 1976
Rats/NR	NR	25	0 or 235 ppm, 7 hours/day, 5 days/week, for 7 weeks	No significant difference from controls in growth, hematological or pathological examination.	LaBelle and Brieger, 1955
Rats/Sherman	M/F	15/sex/ exposure level	0, 125, 250, 500 or 1000 ppm, for 30 days (hours/day and days/week, NR)	No significant histopathological changes in lung, liver or kidney.	Mellon Institute, 1950
Guinea pigs/NR	NR	15	0 or 235 ppm, 7 hours/day, 5 days/week, for 7 weeks	No significant difference from controls in growth, hematological or pathological examination.	LaBelle and Brieger, 1955
Guinea pigs/ mixed strains	M	10/dose level	0, 125, 250, 500 or 1000 ppm, for 30 days (hours/day and days/week, NR)	No statistically significant deviation from controls in body, liver or kidney weights.	Mellon Institute, 1950

*Purity of compound was not reported

NR = Not reported

LaBelle and Brieger (1955) observed no effects of exposure to 235 ppm of methyl ethyl ketone, 7 hours/day, 5 days/week, for 7 weeks, on growth, hematological or pathological parameters of rats and guinea pigs. Likewise, exposure to 0, 125, 250, 500 or 1000 ppm for 30 days had no effect on rats and guinea pigs (Mellon Institute, 1950).

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic oral toxicity of methyl ethyl ketone to humans or experimental animals could not be located in the available literature.

3.2.2. Inhalation. Pertinent data regarding the chronic inhalation toxicity of methyl ethyl ketone to humans or experimental animals could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of methyl ethyl ketone following oral administration could not be located in the available literature.

3.3.2. Inhalation. Schwetz et al. (1974) exposed pregnant Sprague-Dawley rats to methyl ethyl ketone by inhalation at levels of 1000 or 3000 ppm for 7 hours/day on days 6-15 of gestation. There was no maternal toxicity at either exposure level. Somewhat decreased fetal body measurements (body weight and crown-to-rump length) were seen at the lower but not at the higher exposure level. At the 1000 ppm level, a significant increase in litters having fetuses with skeletal abnormalities was seen; however, there was no significant increase in specific gross, soft-tissue or skeletal anomalies. At the 3000 ppm level, a significant increase in litters having fetuses with gross external anomalies or internal soft-tissue anomalies was seen.

3.4. TOXICANT INTERACTIONS

Combined exposure to 100 ppm of n-hexane and 200 ppm of methyl ethyl ketone for 24 weeks resulted in neurotoxic effects (defined as changes in motor nerve conduction velocity, distal motor latency and mixed nerve conduction velocities) in rats that were not observed when either chemical was tested by itself (Takeuchi et al., 1983). Hewitt et al. (1983) found that methyl ethyl ketone potentiated the hepatotoxic response of chloroform in rats. There was a positive significant correlation between the carbon chain length of ketones and the severity of the potentiated chloroform-induced liver damage.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenic effects on humans as a result of oral exposure to methyl ethyl ketone could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenic effects on humans as a result of inhalation exposure to methyl ethyl ketone could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the carcinogenic effects on experimental animals as a result of oral exposure to methyl ethyl ketone could not be located in the available literature. Methyl ethyl ketone is not scheduled for carcinogenicity testing by the National Toxicology Program (NTP, 1983).

4.2.2. Inhalation. Pertinent data regarding the carcinogenic effects on experimental animals as a result of inhalation exposure to methyl ethyl ketone could not be located in the available literature. Methyl ethyl ketone is not scheduled for carcinogenicity testing by the National Toxicology Program (NTP, 1983).

4.3. OTHER RELEVANT DATA

Schwetz et al. (1974) concluded that in rats methyl ethyl ketone is embryotoxic, fetotoxic and potentially teratogenic at exposure levels of 1000 or 3000 ppm by inhalation for 7 hours/day on days 6-15 of gestation. There were no apparent effects on dams at either exposure level.

Pertinent data regarding the mutagenicity of methyl ethyl ketone could not be located in the available literature.

4.4. WEIGHT OF EVIDENCE

Methyl ethyl ketone has not been tested for carcinogenicity by the oral or inhalation routes. No tumors were observed during pathological examinations in subchronic toxicity tests (see Section 3.1.2.). IARC has not evaluated the risk to humans associated with oral or inhalation exposure to methyl ethyl ketone. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating weight of evidence (Federal Register, 1984), no data were available regarding the carcinogenicity of methyl ethyl ketone in humans or animals, and the chemical is most appropriately designated a Group D - Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1983) set a TLV-TWA of 200 ppm (590 mg/m^3) and a STEL of 300 ppm (885 mg/m^3) for methyl ethyl ketone. The basis for these standards is the minimization of eye and nose irritation rather than the prevention of systemic toxic effects (ACGIH, 1980).

The OSHA standard for methyl ethyl ketone is 200 ppm (590 mg/m^3) as an 8-hour TWA for a 40-hour work week (Code of Federal Regulations, 1981).

ACGIH (1980) summarized the standards in other countries as follows: 200 ppm in West Germany (1974); 150 ppm in Sweden (1974); 100 ppm in East Germany (1973); and 100 ppm in USSR (1966), Yugoslavia (1971) and Hungary (1974).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. The lack of subchronic oral toxicity data precludes the derivation of an AIS for subchronic exposure to methyl ethyl ketone.

6.1.2. Inhalation. Several subchronic inhalation studies have been done on methyl ethyl ketone. Two of these studies are not useful for risk assessment, the study by Saida et al. (1976) in which only one toxicological endpoint was evaluated and the study by Mellon Institute (1950) in which complete exposure data were not evaluated and a short duration of exposure (30 days) was used.

A NOEL of 235 ppm for methyl ethyl ketone in rats and guinea pigs can be suggested from the study of LaBelle and Brieger (1955). For identifying the toxic threshold for methyl ethyl ketone, the studies by Cavender et al. (1983) and Takeuchi et al. (1983) are most useful, as both studies define a NOAEL. NOAELs of 2500 ppm of methyl ethyl ketone for increased SGPT activity in female rats (Cavender et al., 1983) and 200 ppm for temporary slight neurological effects in rats (Takeuchi et al., 1983) can be suggested from these studies. A LOAEL of 1000 ppm for skeletal abnormalities in rat fetuses (Schwetz et al., 1974) must also be considered.

The corresponding doses for rats in units of mg/kg/day for the NOEL of 235 ppm (LaBelle and Brieger, 1955), the NOAELs of 200 ppm (Takeuchi et al., 1983) and 2500 ppm (Cavender et al., 1983), and the LOAEL of 1000 ppm (Schwetz et al., 1974) are 107.3, 219.1, 978.1 and 639.0 mg/kg/day, respectively. The equation and calculations are as follows:

$$d_A \text{ (mg/kg/day)} = C \text{ (mg/m}^3\text{)} \times E \text{ (hours/24 hours)} \times D \text{ (days/7 days)} \times IR \text{ (m}^3\text{/day)} \div W_A \text{ (kg)}$$

where

d_A = exposure dose for the experimental animal in units of mg/kg/day;

C = concentration of toxicant in units of mg/m^3;

E = number of hours/day that the animals were exposed divided by 24 hours;

D = number of days/week that the animals were exposed;

W_A = body weight of the experimental animal in kg; and

IR = inhalation rate of the experimental animal in units of m^3/day.

For the NOEL of 235 ppm:

693.1 mg/m^3 x 7 hours/24 hours x 5 days/7 days x 0.26 m^3/day ÷ 0.35 kg = 107.3 mg/kg/day

For the NOAEL of 200 ppm:

589.9 mg/m^3 x 12 hours/24 hours x 7 days/7 days x 0.26 m^3/day ÷ 0.35 kg = 219.1 mg/kg/day

For the NOAEL of 2500 ppm:

7373.8 mg/m^3 x 6 hours/24 hours x 5 days/7 days x 0.26 m^3/day ÷ 0.35 kg = 978.2 mg/kg/day

For the LOAEL of 1000 ppm:

2949.5 mg/m^3 x 7 hours/24 hours x 7 days/7 days x 0.26 m^3/day ÷ 0.35 kg = 639.1 mg/kg/day

The NOAEL of 200 ppm (219.1 mg/kg/day) is chosen to derive an inhalation AIS, as it is the largest NOEL or NOAEL dose that is less than the LOAEL of 1000 ppm (639.0 mg/kg/day) for skeletal abnormalities in rat fetuses. An uncertainty factor of 100 is applied to the animal dose of 219.1 mg/kg/day to convert animal to human data and to protect the more sensitive individuals of a population. This results in an AIS of 2.191 mg/kg/day or 153.4 mg/day for a 70 kg human.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. The lack of chronic oral toxicity data precludes the derivation of an AIC for chronic exposure to methyl ethyl ketone.

6.2.2. Inhalation. There are no chronic studies available from which to derive a chronic inhalation interim ADI for methyl ethyl ketone. The TLV-TWA of 200 ppm (ACGIH, 1983) cannot be used to derive an AIC, as this criterion is based on eye and nose irritation rather than on systemic toxic effects. The subchronic inhalation study by Takeuchi et al. (1983), however, can be used to derive this value. An additional safety factor of 10 must be applied to the AIS of 2.191 mg/kg/day or 153.4 mg/day for a 70 kg human to convert from subchronic to chronic data. This results in an inhalation AIC of 0.2191 mg/kg/day or 15.34 mg/day for a 70 kg human.

An RQ was calculated based on fetotoxicity (Schwetz et al., 1974) observed in rats exposed to methyl ethyl ketone at 1000 ppm (2949 mg/m^3) for 7 hours/day on days 6-15 of gestation. A human MED was calculated by expanding to continuous exposure, assuming a human breathing rate of 20 m^3/day and an absorption efficiency of 0.5, and applying an uncertainty factor of 10 to extrapolate from subchronic to chronic exposure. A human MED of 860.1 mg/day was calculated, corresponding to an RV_d of 1.1. The fetotoxicity observed at this exposure corresponds to an RV_e of 8. A CS of 8.8 is calculated as the product of RV_d and RV_e.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The lack of oral carcinogenicity data precludes the derivation of a carcinogenic potency for oral exposure to methyl ethyl ketone.

6.3.2. Inhalation. The lack of inhalation carcinogenicity data precludes the derivation of a carcinogenic potency for inhalation exposure to methyl ethyl ketone.

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APPENDIX

Summary Table for Methyl Ethyl Ketone

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	rats	200 ppm	temporary slight neurological effects	153.4 mg/day	Takeuchi et al., 1983
AIC	rats	200 ppm	temporary slight neurological effects	15.34 mg/day	Takeuchi et al., 1983
Maximum composite score	rats	1000 ppm (2949 mg/m^3), 7 hours/day on days 6-15 of gestation (RV_d=1.1)	fetotoxicity (Rv_e=8)	8.8	Schwetz et al., 1974
Oral					
AIS	NA	NA	NA	ND	NA
AIC	NA	NA	NA	ND	NA

NA = Not applicable; ND = not derived